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ORIGINAL ARTICLE

Study of Serum Fibroblast Growth Factor 23 and Its Relation to Insulin Resistance in Obese Patients

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ABSTRACT

Background: The prevalence of obesity has risen substantially in developing and western countries. Obesity presents a major problem leading to cardiometabolic consequences including insulin resistance (IR) and metabolic syndrome. Fibroblast growth factor 23 (FGF-23) plays a role in the metabolism and phosphate mineralization. The aim of the study was to investigate the relationship between IR, serum FGF23 alongside obesity in affected individuals.

Methods: This is a case control study included 60 obese patients (BMI > 30 kg/m²) and 30 healthy controls. All participants underwent thorough history taking, clinical examination and laboratory investigations. Serum FGF-23 was measured, and IR was calculated using the Homeostatic Model Assessment of IR (HOMA-IR) in both groups.

Results: Serum levels of FGF 23 were significantly elevated in obese patients (mean 46.97 ± 40.40 pg/ml) compared to controls (mean 40.97 ± 43.16 pg/ml) ($p<0.001$). Moreover, obese patients showed significantly higher HOMA-IR values than controls ($P =0.009$). Multivariate regression analysis revealed age ($p=0.009$), low-density lipoprotein (LDL) ($p=0.002$), and C-reactive protein (CRP) ($p=0.042$) as statistically significant parameters for obesity while gender ($p=0.418$) did not reach statistical significance.

Conclusions: This study demonstrates that obese patients had significantly higher serum FGF23 levels and increased HOMA-IR values than non-obese. The multivariate analysis displayed age, LDL and CRP as predictors of obesity indicating their role in metabolic dysfunction associated with obesity. These findings suggest that FGF23 and IR play a part in obesity so further research of their mechanisms is necessary. Targeted interventions aimed at these factors may reduce health risks of obesity.

Key words: FGF23, obesity, insulin resistance (IR), HOMA-IR, cardiometabolic risk

INTRODUCTION

Obesity is associated with a growing number of chronic diseases, presenting a significant worldwide public health problem. The prevalence of obesity has risen globally over the past few decades, and it is currently one of the World Health Organization's noncommunicable disease objectives [1]. The overall obesity prevalence has grown dramatically reaching up to 5 % in children and 12 % in adults worldwide [2,3]. Obesity creates major personal, health care and social burden mainly through cardiometabolic complications including insulin resistance (IR), type 2 diabetes and cardiovascular disease [4].

FGF23 is the primary hormone that regulates the levels of circulating phosphate. It

indirectly regulates phosphate homeostasis by modifying intestinal phosphate absorption and urine phosphate excretion. This is achieved by downregulating the expressed renal and intestinal sodium phosphate transporters. Evidence suggested that FGF23 has a "hormone-like" factor role in both glucose as well as lipids metabolism in addition to playing a substantial part in the pathophysiology of calcium-phosphorus disorders [5]. Recent research indicates that bone osteocytes produce the hormone FGF-23, which is then involved in the kidney's phosphate metabolism and, eventually, bone mineralization [6]. Research data show that adipokines and bone derived factors interact with fat to create a homeostatic feedback loop in adipokines in the bone-adipose metabolic axis, suggesting the involvement of the bones in the homeostatic processes, governing energy balance and fat metabolism [7]. FGF23 has been linked to indicators of insulin resistance (IR), dyslipidemia, and visceral obesity in both adult and paediatric populations. These results suggest its potential role as a partial mediator between metabolic dysfunction and cardiovascular disease (CVD) [8].

The relationship between insulin resistance and FGF23 is complicated. While some research did not show a correlation, many investigations found that diabetes was linked to higher serum levels of FGF23. It is evident that inflammation plays a significant role in the production of FGF23, and many type 2 diabetic patients—particularly those who are obese—have inflammatory conditions [9-11].

The aim of the study was to investigate the relationship between FGF-23 concentrations and obesity-related metabolic conditions such as insulin resistance (IR) and cardiometabolic risk factors. This research examines the bone-adipose endocrine axis and its effects on metabolic dysregulation that occurs with obesity.

METHODS

This work had been approved by the ethical committee of the internal medicine department of faculty of medicine, Alexandria University on 17th of September 2020, serial number: 0106515. All study involved patients provided informed consent, and the principles of the Helsinki Declaration were observed. A consent for publication was taken from the participants.

This is a case control study including 60 patients with simple obesity admitted to the Endocrinology clinic or the inpatient Internal Medicine Department, Endocrinology unit, at Alexandria Main University Hospital and 30 healthy individuals as a control group.

The study excluded patients with diabetes mellitus, chronic renal diseases, chronic hepatic diseases, patients with any disorders of calcium–phosphorus metabolism. A full history and physical examination were performed on each patient who fulfilled the requirements, including:

Anthropometric and biochemical assessments:

Body weight and height were measured; BMI was calculated as weight (kg)/height2 (m2). Waist circumference was obtained at the midpoint between the lowest rib and the iliac bone. Hip circumference (HC) and waist-hip ratio (WHR) were measured.

Samples of venous blood were collected from the antecubital vein and placed into plain vacuum-tight containers. Sampling was done after spending about 10 hours fasting overnight. Centrifugation was done to separate the serum from obtained venous samples at least 30 minutes after sampling.

Using automated chemistry or immunoassay analyzers, fasting glucose levels (FBG), renal function tests, serum CRP, serum calcium, and serum phosphorus were measured. Serum triglycerides (TG) and low-density lipoprotein (LDL) comprise the lipid profile. Tests for thyroid function included measuring free tetraiodothyronine (FT4) and serum thyroid stimulating hormone (TSH) were assessed.

Finally, insulin resistance (IR) was calculated using the Homeostatic Model Assessment of IR using the following formula: HOMA-IR = Glucose (mg/dl) X Insulin /405. Serum FGF-23 was measured in both groups by the enzyme-linked immunoassay (ELISA).

Test principle of ELISA

Based on the Sandwich-ELISA concept, the ELISA kit was utilized to quantify the FGF23. The micro-ELISA plate was precoated with an anti-human FGF23

antibody. Samples are then mixed with species-specific antibodies within the wells on the micro-ELISA plate. Following the addition of each microplate, it was then incubated. Avidin-horseradish peroxidase (HRP) conjugate with the human FGF23-specific biotinylated detection antibody was incubated together within each well of the micro-ELISA plate. Washing was done to remove the free solution that remained. Each well was filled with the added substrate solution. Blue coloration resulted only in wells that included Avidin-HRP conjugate, Biotinylated Detection Antibody, and Human FGF23. The yellow color change indicated the termination of the enzyme-substrate reaction following the stop solution addition. Ultimately, spectrophotometric optical density (OD) measurements at 450 nm ± 2 nm were made. The OD obtained value corresponds to the concentration of the human FGF23.

Statistical analysis

IBM SPSS version 20.0 software analyzed the data that was input into the computer. IBM Corp. (Armonk, New York). The qualitative data was illustrated by numbers and percentages. Using the Kolmogorov-Smirnov test is required to confirm that the data was normally distributed. The qualitative data was described using the following: mean, median, and range (minimum and maximum). The results proved to be significant at the 5% level. The tests employed during this study were:

1 - Chi-square test

To compare categorical variables in both groups.

2 - Student t-test

For comparing two involved study groups using their obtained quantitative variables that are normally distributed.

3 - Mann Whitney test

For comparing the two involved research groups using their obtained with non-quantitative variables that are normally distributed.

4 - Pearson coefficient

Correlating two quantitative variables with a normal distribution.

RESULTS

Clinical and laboratory characteristics of participants:

The study comprised 60 patients with simple obesity (16 males, 44 females; mean age 39.32 ± 11.25 years; mean BMI 36.02 ± 5.13) and 30 healthy controls (mean BMI 22.08 ± 1.76). In the obese patients, 15 were smokers (25%), 44 non-smoker (73.3%) and one patient was ex-smoker (1.16%). Compared to controls, the obese group had significantly higher systolic blood pressure (p=0.028), FBG (p=0.004), BMI, waist circumference (WC), and waist-to-hip ratio (WHR) ($p < 0.001$) (Tables 1,2). Additionally, obese individuals exhibited elevated serum levels of CRP, LDL, triglycerides (TG) ($p < 0.001$), and HOMA-IR ($p = 0.019$), along with lower urea and creatinine levels ($p < 0.001$). No other significant differences were observed between the groups (Table 2).

Serum TG concentrations strongly correlated with BMI. Significant associations were also found between BMI and both WC and hip circumference (HC), with a notable relationship between WC and HC. Multiple regression analysis identified age, WC, HC, WHR, HOMA-IR, LDL, TG, and CRP as significant predictors of obesity.

Comparison of serum FGF23 levels:

Serum FGF23 levels were significantly higher in the obese group (mean 46.97 ± 40.40) compared to controls (mean 40.97 ± 43.16; $p < 0.001$) (Table 3, Figure 1).

Univariate and Multivariate Regression Analyses of Obesity Predictors:

In the univariate regression analysis, the following variables emerged as significant predictors of obesity: female gender ($p = 0.014$), age ($p < 0.001$), waist circumference (WC, $p = 0.040$), hip circumference (HC, $p = 0.002$), waist-to-hip ratio (WHR, $p = 0.001$), HOMA-IR ($p = 0.020$), urea ($p < 0.001$), creatinine ($p < 0.001$), LDL ($p < 0.001$), triglycerides (TG, $p < 0.001$), and CRP ($p < 0.001$).

In the multivariate regression analysis, only age ($p = 0.009$), LDL ($p = 0.002$), and CRP ($p = 0.042$) remained significant predictors, while female gender showed a non-significant association ($p = 0.418$) (Table 4).

Table 1: Comparison between obese patients and controls according to anthropometric measurements

	Obese patients (n=60)	Control group (n=30)	Test of sig.	p-value
Systolic (mmHg)	100.0 – 140.0	100.0 – 120.0		
Min. – Max.	117.7 ± 8.58	111.2 ± 5.77	2.21	0.028*
Mean ± SD				
Diastolic (mmHg)				
Min. – Max.	60.0 – 90.0	60.0 – 80.0	1.075	0.85
Mean ± SD	76.0 ± 6.75	76.8 ± 6.51		
BMI (kg/m^2)				
Min. – Max.	30.0 – 54.0	19.0 – 24.80	18.929 *	<0.001*
Mean ± SD.	36.02 ± 5.13	22.08 ± 1.76		
Median (IQR)	35.0 (32.0 – 38.0)	22.0 (21.0 – 24.0)		
Circumference of Waist (cm)				
Min. – Max.	90.0 – 110.0	80.0 – 91.0	15.329 *	<0.001*
Mean ± SD.	98.27 ± 6.02	83.50 ± 3.12		
Median (IQR)	97.0 (94.0 – 104.0)	83.0 (81.0 – 85.0)		
Hip circumference (cm)				
Min. – Max.	96.0 – 116.0	88.0 – 99.0	15.360 *	<0.001*
Mean ± SD.	107.3 ± 5.30	94.43 ± 2.65		
Median (IQR)	107.0 (102.0 – 112.0)	95.0 (92.0 – 96.0)		
Ratio				
Min. – Max.	0.84 – 0.98	0.85 – 0.98	3.758*	<0.001*
Mean ± SD.	0.92 ± 0.04	0.89 ± 0.03		
Median (IQR)	0.92 (0.89 – 0.94)	0.88 (0.86 – 0.91)		

IQR: Inter quartile range, SD: Standard deviation, f: ANOVA, t: Student t-test, χ^2: Chi square test, p*: Statistical significance p value indicated at $p \leq 0.05$

Table 2: Laboratory and hormonal parameters of the studied groups

	Obese patients (n = 60)	Controls (n = 30)	Sig. Test	p-value
Glycemic parameter				
FBG (mg/dl)				
Min. – Max.	58.0 – 118.0	70-90	t= 3.03	0.004*
Mean ± SD.	86.52 ± 14.21	77.88 ± 6.45		
Median	88.0	77		
HOMA-IR				
Min. – Max.	0.20 – 31.0	0.50 – 3.0	U = 626.50*	0.019*
Mean ± SD.	4.29 ± 5.86	1.73 ± 0.61		
Median (IQR)	2.35 (1.25 – 4.3)	1.70(1.30 – 2.0)		
Renal function				
Urea				
Min. – Max.	17.0 – 45.0	25.0 – 41.0	t = 4.651*	<0.001*
Mean ± SD.	27.18 ± 6.72	32.73 ± 4.49		
Median (IQR)	27.0 (21.50 – 31.0)	32.0 (29.0 – 37.0)		
Creatinine			U = 443.50*	
Min. – Max.	0.20 – 1.10	0.70 – 1.10		<0.001*
Mean ± SD.	0.73 ± 0.20	0.90 ± 0.13		
Median (IQR)	0.74 (0.64 – 0.90)	0.90 (0.80 – 1.0)		

	Obese patients (n = 60)	Controls (n = 30)	Sig. Test	p-value
Calcium (mg/dl)				
Min. – Max.	7.80 – 10.70	8.0 – 10.90	t = 0.802	0.427
Mean ± SD.	9.56 ± 0.62	9.43 ± 0.81		
Median (IQR)	9.50 (9.2 – 10.0)	10.0 (9.0 – 10.0)		
PO4 (mg/dl)			U = 891.50	
Min. – Max.	2.10 – 4.40	2.50 – 4.10		0.942
Mean ± SD.	3.37 ± 0.50	3.36 ± 0.50		
Median (IQR)	3.40 (3.0 – 3.8)	3.50 (2.9 – 3.7)		
Lipid profile				
LDL(mg/dl)				
Min. – Max.	26.0 – 206.0	61.0 – 127.0	U= 176.50*	<0.001*
Mean ± SD.	110.7 ± 32.89	71.93 ± 11.51		
Median (IQR)	107.0 (90.5 – 135.0)	70.0 (66.0 – 74.0)		
TG (mg/dl)				
Min. – Max.	34.0 – 355.0	52.0 – 90.0	U= 435.50*	<0.001*
Mean ± SD.	135.9 ± 72.32	74.67 ± 9.95		
Median (IQR)	120.0 (74.5 – 178.5)	75.0 (69.0 – 84.0)		
Thyroid function				
TSH (uIU/ml)			U = 696.0	
Min. – Max.	0.58 – 4.50	1.0 – 4.0		0.081
Mean ± SD.	1.85 ± 0.91	2.22 ± 0.93		
Median (IQR)	1.67 (1.2 – 2.1)	2.0(1.40 – 3.20)		
FT4 (ng/dl)				
Min. – Max.	0.89 – 1.74	0.90 – 1.60	t = 1.122	0.265
Mean ± SD.	1.20 ± 0.23	1.26 ± 0.22		
Median (IQR)	1.20 (0.99 – 1.3)	1.25 (1.1 – 1.4)		
CRP (mg/l)				
Min. – Max.	0.50 – 130.0	1.0 – 4.50	U= 290.50*	<0.001*
Mean ± SD	8.98 ± 17.23	2.02 ± 0.75		
Median (IQR)	4.35 (3.0 – 9.0)	1.90 (1.5 – 2.6)		

IQR: Inter quartile range, SD: Standard deviation, t: Student t-test, U: Mann Whitney test, p*: Statistical significance p value indicated at $p \leq 0.05$

Table 3: Comparison of serum FGF23 levels between obese patients and controls

FGF 23 (pg/ml)	Obese patients (n = 60)	Controls (n = 30)	Test Mann Whitney	p-value
Min. – Max.	25.0 – 246.0	16.0 – 197.0	397.00*	<0.001*
Mean ± SD.	46.97 ± 40.40	40.97 ± 43.16		
Median (IQR)	36.0 (32.0 – 43.5)	27.0 (20.0 – 31.0)		

p: p value to compare the study involved groups, *: Statistical significance at $p \leq 0.05$

Table 4: Univariate and multivariate logistic regression analysis of factors associated with obesity (cases = 60, controls = 30).

	Univariate		#Multivariate	
	p	OR (95% C.I)	P	OR (95% C.I)
Female	**0.014***	3.143 (1.256 – 7.867)	0.418	2.342 (0.299 – 18.339)
Age (years)	**<0.001***	1.214 (1.091 – 1.349)	0.009*	1.255 (1.060 – 1.487)
BMI (kg/m^2)	**0.993**	–		
Waist circumference	**0.040***	5.368 (1.079 – 26.713)		

(cm)				
Hip circumference (cm)	**0.002***	3.516 (1.588 – 7.784)		
Ratio	**0.001***	11.645$ (2.757 – 49.182)		
FBG	**0.167**	0.976 (0.944 – 1.010)		
HOMA-IR	**0.020***	1.616 (1.078 – 2.423)		
Urea	**<0.001***	0.859 (0.788 – 0.935)		
Creatinine	**<0.001***	0.558$ (0.403 – 0.772)		
Calcium	**0.381**	1.329 (0.704 – 2.508)		
PO_4	**0.904**	1.056 (0.435 – 2.562)		
LDL	**<0.001***	1.083 (1.043 – 1.124)	0.002*	1.100 (1.036 – 1.168)
TG	**0.001***	1.034 (1.014 – 1.054)		
TSH	**0.077**	0.653 (0.407 – 1.047)		
FT4	**0.263**	0.330 (0.048 – 2.293)		
CRP	**<0.001***	2.483 (1.514 – 4.073)	0.042*	2.130 (1.028 – 4.415)
FGF 23	**0.519**	1.004 (0.992 – 1.016)		

OR: Odd`s ratio, $: for each 0.1 Ratio, C.I: Confidence interval, LL: Lower limit, UL: Upper Limit, #: Multivariate analysis included all factors with p<0.05., *: Statistical significance indicated at p ≤ 0.05

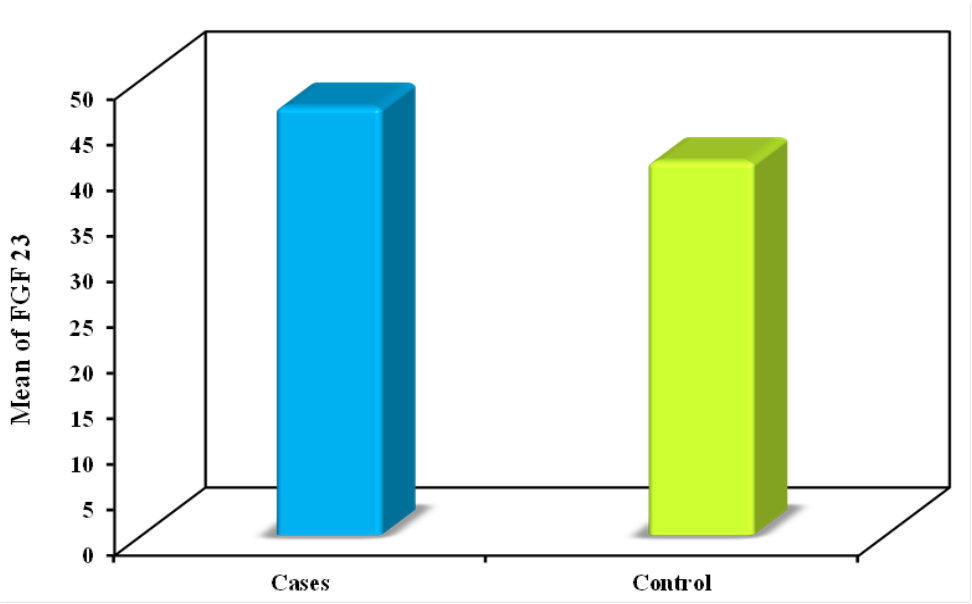

Figure 1: Comparison between the two studied groups according to FGF 23

DISCUSSION

The hormone FGF23 functions primarily to regulate calcium and phosphorus metabolism yet it exhibits additional hormone-like effects on lipid and carbohydrate metabolism. Research about the relationship between FGF23 and the development of metabolic problems through atherogenic lipid fractions and obesity has shown conflicting results. Some research found a positive correlation between FGF23 and body weight or fat tissue content [12]. On the contrary, other studies reported an inverse relationship between FGF23 and atherogenic lipid fractions [13]. These findings raise questions regarding the precise mechanism through which FGF23 contributes to metabolic syndrome development. The aim of the study was to explore these associations in simple obesity individuals.

The present study showed that obese patients had elevated FGF-23 serum levels than

controls in accordance with findings from a large-scale study which involved 1,599 participants and concluded that fat rises FGF23 levels [14]. Our study supported previous research findings by Ali et al. [15], Xu et al. [16], and Gutiérrez et al. [17] which established a link between obesity and elevated FGF-23 levels.

An increasing amount of data suggested that bone was involved in homeostasis management, encompassing adipose tissue metabolism and energy balance. A feedback mechanism of homeostasis was constructed between bone and adipose tissue through their interaction with adipocytokine and bone-derived factor [18]. It has been proposed that FGF23, a protein primarily generated and secreted by osteoblasts/osteocytes, regulates the distribution and accumulation of fat. Clinical studies showed a correlation between FGF23 and central obesity as well as total obesity. More specifically, 3% of the changes in trunk fat mass and 2% of the variability in total fat mass were explained by FGF23. It was proposed that elevated fat mass and the emergence and progression of the metabolic syndrome and its elements were associated with circulating FGF23 [12].

Our data showed obese participants displayed elevated CRP values compared to control group. Likewise, a study by Anne-Cecile Paepegaey et al. investigated the correlations between CRP and many biochemical indicators as well as the histologic characteristics of the liver and subcutaneous and omental white adipose tissue (scWAT) in 674 obese patients (mean BMI = 47 ± 7.4 kg/m2). The CRP had a mean of 8.9 ± 6.9 mg/L and showed a positive correlation with fat mass. The research establishes white adipose tissue (WAT) inflammation as the primary cause of elevated CRP values seen in obesity [19]. J. Choi, L. et al. used a meta-analysis and systematic review to evaluate the relationships between obesity and CRP by age, sex, and ethnicity. The databases MEDLINE and EMBASE were searched up until October 2011. Obesity and increased CRP levels were clearly correlated in every studied population [20]. Another cross-sectional study included one hundred Koreans without a history of cancer or inflammatory disorders. Measurements of WC, serum CRP, TNF-, and IL-6 concentrations, and BMI were performed. The median CRP for the non-obese group was 0.22 (0.20-0.38) mg/dl, while it was 1.05 (1.03-2.36) mg/dl for the obese group. Obese individuals exhibited noticeably increased CRP ($P < 0.05$) [21].

This study found that obese patients had higher levels of LDL and triglycerides significantly compared to controls. A case control study by Mohammed Khaleel and Muhammad N Khan involved showed that cholesterol and triglycerides were higher in obese people than non-obese [22] which confirms the link between obesity and adverse lipid profiles.

In our study, a noteworthy association was observed between HOMA-IR and obesity. On the other hand, there was no significant correlation between FGF23 and HOMA-IR. This research agrees with a study from the Bambino Gesù Children's Hospital which measured 2,573 Caucasian children and adolescents during 2012–2013 to find significantly higher HOMA-IR values among overweight/obese children compared to normal-weight children ($P < 0.0001$) [23].

Furthermore, in a pooled analysis of the Osteoporotic Fractures in Men and the Prospective Investigation of the Vasculature in Uppsala Seniors investigations, Mirza and colleagues failed to discover an independent correlation of FGF23 with HOMA-IR [24].

In contrast to our findings, a study by Malgorzata Wojcik et al demonstrated the presence of a correlation between FGF23 level and insulin sensitivity in obese patients, they showed an inverse correlation between FGF23 and HOMA-IR. However, these correlations were very low to prove the direct effect of FGF23 on insulin resistance [25].

The inconsistent results may result from phosphate homeostasis dependency on FGF23 cofactor Klotho [26]. Klotho-FGF23 interaction plays a critical role in phosphate regulation. The gene polymorphisms of Klotho have been shown to independently link with metabolic syndrome pathogenesis and insulin resistance [27]. The exact mechanism through which increased visceral adiposity produces elevated circulating FGF23 levels remains unknown. A study by

Streicher et al demonstrated that FGF23 knockout mice had unique changes in the body composition (higher levels of ash/protein and decreased fat content), however in mice with FGF23/vitamin D receptor multiple mutations, body weight and body composition were like those of mice of the wild type [28]. This foundational study proposed that the regulation of FGF23 in the distribution and storage of fat is mediated by a mechanism dependent on the vitamin D receptor. Additionally, research in animals has shown the adipokines' stimulatory effects on bone FGF23 expression, indicating that adipose tissue has a feedback impact on serum FGF23 levels [29].

Another study showed strong evidence that insulin is a potent and clinically significant inhibitor of FGF23 production in both mice and humans. Their findings indicate that FGF23 gene transcription is down-regulated as a result of insulin-induced suppression of the transcription factor FOXO1 via PI3K/PKB/Akt signalling [31]. Acute hyperinsulinemia has even been shown to raise FGF23 levels in patients with type 2 diabetes, indicating that intact insulin signalling is necessary for insulin to suppress FGF23 secretion [32]. This idea is supported by the observation that FGF23 serum levels are higher in insulin-resistant people [33].

Strengths of the study lies in involvement of a specific population with simple obesity to avoid confounding conditions in addition to controls with matched age and sex to reduce bias and increase the clinical value of observed results. The study provides a complete metabolic profile analysis of obesity-related markers (FGF23, CRP, lipid profile, HOMA-IR) which gives a comprehensive understanding of metabolic dysregulation. The research results match those of large-scale studies (elevated CRP, LDL, and FGF23 in obesity) which confirms the accuracy of our research findings. The research used univariate and multivariate regression methods to establish independent obesity predictors which improved statistical reliability.

The limitations of the study include assessment of selected biochemical parameters while we agree that a comprehensive assessment of bone adipose endocrine axis would include additional markers. Future studies are recommended to incorporate HbA1c for more comprehensive dysglycemia assessment. Further studies with larger sample size are needed to explain the presence of higher levels of FGF23 in obese individuals, and its association with insulin sensitivity as well as to clarify the causal relation of serum FGF23 levels with fat content and distribution.

CONCLUSIONS

The present study demonstrates that obese individuals have elevated levels of FGF23, CRP, LDL, TG and HOMA-IR compared to healthy controls confirming that obesity is a risk for metabolic dysfunction. Elevated levels of FGF23 in obesity suggests a potential role linked to adipose tissue and insulin resistance extending beyond mineral metabolism. Further research is required to define the exact mechanism. Multivariate regression analysis showed that age, WC, LDL and CRP are independent predictors for obesity emphasizing the link between adiposity, dyslipidemia and chronic inflammation.

Compliance With Ethical Standards: This work had been approved from the ethical committee of the internal medicine department of faculty of medicine, Alexandria University. All study involved patients provided informed consent, and the principles of the Helsinki Declaration were observed. A consent for publication was taken from the participants.

Conflicts Of Interest: There are no relevant financial or non-financial interests to report for the authors. The authors state that they do not have any conflicts of interest.

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Author Contributions: The study was designed by MASA and AAE. The data was obtained by MASA and BAMI. MASA, BAMI and MMT analyzed and interpreted the

data. MASA and BAMI wrote the text. All authors revised the written manuscript, approved the final version, and assumed responsibility for the data analysis's integrity. The authors claim that the manuscript is unique and has never been published before. Each author affirms that he or she made a major contribution to the work detailed in the manuscript and its preparation.

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Citation

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